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Subjective and Objective Measures of Dryness Symptoms in Primary Sjögren's Syndrome – Capturing the discrepancy

Short title: Objective signs and subjective symptoms in Sjögren's

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Abstract

Background: There is a weak relationship between subjective symptoms and objective markers of disease activity in individuals with Primary Sjögren's Syndrome (PSS). This presents a significant barrier to developing treatments if modifying disease markers does not translate into reduced perception of symptoms. Little is known about the reasons for this discrepancy.

Objectives: To develop a novel method for capturing the discrepancy between objective tests and subjective dryness symptoms (a 'Sensitivity' scale) and to explore predictors of dryness Sensitivity.

Methods: Archive data from the UK Primary Sjogren's Syndrome Registry (n=681) was used. Patients were classified on a scale from -5 (stoical) to +5 (sensitive) depending on the degree of discrepancy between their objective and subjective symptoms classes. Sensitivity scores were correlated with demographic variables, disease-related factors and symptoms of pain, fatigue, anxiety and depression.

Results: Patients were on average relatively stoical for both dryness symptoms (ocular mean \pm s.d. -0.42 ± 2.2 , oral mean \pm s.d. -1.24 ± 1.6). Twenty-seven percent of patients were classified 'sensitive' to ocular dryness in contrast to 9% for oral dryness. Hierarchical regression analyses identified the strongest predictor of ocular dryness was self-reported pain and the strongest predictor of oral dryness was self-reported fatigue.

Conclusions: Ocular and oral dryness sensitivity can be classified on a continuous scale. The two symptom types are predicted by different variables. A large number of factors remain to be explored that may impact on symptom-sensitivity in PSS and the proposed method could be used to identify relatively sensitive and stoical patients for future studies.

Key words:

Primary Sjögren's Syndrome, dryness symptoms, subjective objective discrepancy, Schirmer's I Test, Unstimulated Salivary Flow

Significance and Innovations:

- Outlines a novel method for defining concordance between objective signs and subjective symptoms that is independent of units of measurement
- The method is able to identify both stoical individuals (high objective signs, low subjective symptoms) and sensitive individuals (low objective signs, high subjective symptoms)
- We explored factors predicting symptom sensitivity – pain and fatigue symptoms were the biggest predictors of sensitivity to ocular and oral dryness respectively
- A large proportion of variance in symptom sensitivity remains unexplained – this method could be used in future studies to identify sensitive individuals and investigate a larger number of predictive factors (including further biological and psychological measures)

Primary Sjögren's Syndrome (PSS) is an autoimmune disorder of unknown aetiology which is characterised by dry eyes and dry mouth and is associated with extraglandular systemic symptoms such as fatigue, pain (myalgia and polyarthralgia) and autonomic dysfunction (1). It has an estimated prevalence of 0.01 - 0.09% (2) and is more common in women (9:1 female:male ratio (3)). The condition has a marked negative impact on health-related quality of life and social functioning (4)

The medications used to improve extraglandular symptoms are less effective in treating sicca symptoms (5). An important factor in understanding and treating these is the weak association between the results of objective clinical tests of tear or saliva production and the severity of self-report dryness symptoms. This is reflected in the current America European Consensus Group (AECG) classification criteria, which dictate that a PSS diagnosis is made when individuals fulfil four or more of the established criteria, which include both subjective and objective items (6).

Understanding the discrepancy between objective and subjective findings may be of importance for improving research into the condition.

Several studies have indicated weak correlations between objective and subjective indices of ocular dryness (7-15). Although the majority of these studies found that subjective symptoms are generally worse with increased objective severity, two observed that subjective symptoms were better as the objective severity measure increased (7, 15), which may relate to reduced sensation resulting from greater damage to the eye (7). In contrast, the relationship between subjective and objective oral dryness measures seems to be stronger (16-21), although there are some individuals suffering from subjective xerostomia who display no objective salivary

gland dysfunction (17).

Discrepancies between objective and subjective symptoms create a number of dilemmas for clinicians. For example, patients may not receive optimal treatment (those with abnormal test results but few subjective symptoms may be 'under-treated', whereas those with normal test results but high subjective symptoms may receive interventions that are unlikely to help). Furthermore it becomes difficult to interpret (lack of) response to treatment, which could be particularly important in clinical trials of novel therapeutic agents. It is therefore of interest to explore this relationship in greater depth. The path from pathological change in tissues to perceived distressing symptoms is complex and dependent on a number of factors both relating to the severity of the underlying disease as well as concomitant psychosocial factors including low mood and anxiety (22-26). Developing a method to differentiate patients on the basis of their sensitivity to symptoms could aid research into the factors that contribute to variability in the distress and disability caused by PSS and ultimately could contribute to the stratification of patients for particular management pathways.

The present study develops a novel method to define the degree of concordance/discrepancy between objective and subjective findings. This will be used to investigate the relationship between subjective symptoms and objective measures of dry eyes and mouth in people with PSS to identify factors associated with symptom sensitivity.

Patients and Methods

Participants

The present study uses archive data from 688 patients on the United Kingdom Primary Sjögren's Syndrome Registry database (UKPSSR, www.sjogrensregistry.org), who were recruited across 30 hospital sites from August 2009 to March 2012 (for full details see (27)). All patients fulfilled the AECG classification criteria (6). Patients gave written informed consent to participate and National Health Service ethical approval was granted for this study from North West – Haydock National Research Ethics Service committee.

Measures

Patient-Reported Measures

Subjective symptoms were assessed using the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESS PRI) sicca scores. This is a validated self-report measure of ocular and oral dryness symptoms (28, 29). Patients rated their symptoms over the past two weeks on a 0-10 scale (10=maximum imaginable dryness). In addition, there were also items that measured subjective fatigue, mental fatigue and pain. Patients also self-reported their medication use and comorbidities.

Psychosocial factors

The EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) (30) was used to measure quality of life (QoL). This includes a simple Visual Analogue Scale (VAS) and a Time Trade Off value (TTO). Lower values indicate better quality of life.

Depression and anxiety were measured using the Hospital Anxiety and Depression scales (HADS) (31).

Clinician-reported Assessment Measures

The ESS Disease Activity Index (DAI) (29, 32) and Disease Damage Index (DDI) (33) were used to assess the extent of systemic disease activity and damage respectively.

Ocular dryness

Schirmer I test: A sterile strip of filter paper was inserted inside the patient's lower eyelid for 5 minutes after which, the level of wetting was measured using a standardised ruler. The average result of both eyes was then calculated. Participants were asked not to use eye-drops for 2 hours prior to testing. Lower scores indicate abnormal tear production and a score of $\leq 5\text{mm}/5\text{min}$ is considered severe by AECG criteria (6).

Oral dryness

Unstimulated Salivary Flow (USF): the patient was required to spit saliva into a graduated test tube every minute. This was conducted under normal room temperature and humidity and participants were asked not to eat/drink/smoke for at least 2 hours beforehand. According to AECG criteria, a quantity of $\leq 1.5\text{ml}$ collected over 15 minutes indicates impaired saliva secretion (6).

Defining Discordance

The present study used a modified discordance measure that was based on Delbaere et al. (34)(2010). Subjective symptom severity and objective test result severity for both ocular and oral dryness were split into classes. Patients' subjective ocular and oral dryness severities (based on ESS PRI item scores) were grouped into

asymptomatic (scoring 0) and symptomatic groups (5 equal classes; see Table 1).

Objective test result severities were grouped into the same number of classes. As no formal severity “grading” is available for either the Schirmer’s test or USF results, reasonable severity “grading” cut-offs, supported by the expert consensus of a consultant rheumatologist, were established for the purposes of this study and test results were grouped into equal severity classes as shown in Table 1. The severe class cut-offs, for both Schirmer and USF tests, are as close as possible to the diagnostic cut-offs used by the AECG criteria.

The subjective severity classes for ocular and oral dryness were then cross-tabulated with the corresponding objective severity class in order to identify each patient’s degree of sensitivity for ocular and oral dryness. This was completed using the sensitivity grid shown in table 1.

The degree of disparity between subjective symptoms and objective test results was given an arbitrary value and conceptualised on a continuous Sensitivity scale (see figure 1). On the scale a value of 0 signifies full concordance, with negative values indicating increasing stoicism and positive values indicating increasing sensitivity. Patients were grouped into ‘sensitive’ (a positive sensitivity score), ‘accurate’ (a score of 0), and stoical (a negative sensitivity score).

Analysis

Analyses were performed using IBM SPSS/PC software version 21. Pairwise deletions for missing data were employed. One-way ANOVA with post-hoc least significant difference tests were used to compare groups, using $\alpha=0.05$. Proportion data

between groups was compared with chi-square tests, with any significant overall difference followed-up with pairwise comparisons with a Bonferroni-adjusted p-value of $p=0.05/3=0.017$. Bivariate Spearman correlations were used to explore the relationships between objective and subjective measures and between Sensitivity and demographic variables, disease- and treatment-related factors, and self- and clinician-rated symptoms. The strength of correlations was compared using Fisher's r to z transformation. Linear stepwise hierarchical multiple regression was used to explore the predictors of Sensitivity. Variables were entered stepwise in the following sequence of blocks: 1) demographics and disease factors (age, gender, symptom duration, disease damage index, number of comorbidities, number of medications, number of xerogenic medications, use of a lachrymal/saliva substitute), 2) Other symptoms and quality of life (fatigue, mental fatigue, pain, anxiety, depression and quality of life visual analogue scale). The criteria for entry into the model was $p<0.05$ and for exit $p>0.1$. Separate regressions were run for ocular and oral sensitivity. Only the results for the variables appearing in the final model are reported.

Results

Participant characteristics and scores on the measures are reported in table 3. The majority of the sample was female ($n=651$ (95%)). Lachrymal and saliva substitutes were used by 544 (79.1%) and 305 (44.3%) participants respectively. Two hundred and ninety five participants (42.9%) were taking at least one xerogenic medication.

Subjective vs Objective Symptoms

A weak but significant correlation ($r=-0.13$, $p=0.001$) was found between ocular dryness and Schirmer test results. A moderate correlation ($r=-0.31$, $p<0.001$) was found between oral dryness and USF test results. The directions of the relationships indicate that increasing symptom severity was associated with reduced tear and saliva production. Objective and subjective results were significantly more strongly correlated for oral dryness than ocular dryness ($z=3.47$, $p<0.001$).

Symptom Severity and Sensitivity

Table 1 shows the proportion of patients falling into the 6 severity classes on each of the objective measures. Forty-six percent of patients were in the most severe range for the Schirmer test and 77% for unstimulated salivary flow, indicating markedly reduced saliva production was more common than markedly reduced tear production. Sixteen percent of patients were in what we have defined as the 'normal' range for the Schirmer test compared with only 4% for unstimulated salivary flow. Cross-tabulating ocular and oral severity gradings showed that only eight people (1.2%) were in the 'normal' range on both measures, whereas 268 (39.4%) were in the most severe classification for both. In this sample, a high proportion of patients had severe symptoms on at least one objective test measure.

A level of discordance (i.e. a Sensitivity score other than zero) was observed in 80.9% and 73.7% of the participants for ocular and oral dryness respectively. Mean ocular Sensitivity was -0.42 (s.d.=2.2) and mean oral Sensitivity was -1.24 (s.d.=1.6), indicating on average patients were relatively stoical for both dryness symptoms. Fewer patients scored in the sensitive range (score $\geq +1$) for oral dryness ($n=59$, 8.7%) than ocular dryness ($n=178$, 26.8%). This is partly related to differences in the

severity of objective results – the majority of patients had severely reduced saliva production, and therefore could not score in the sensitive range.

Sensitivity for ocular and oral dryness were positively correlated ($r = 0.35$, $p < 0.001$), indicating that a higher sensitivity for ocular dryness was associated with higher sensitivity for oral dryness.

Factors influencing ocular and oral dryness sensitivity

Table 3 reports means by group for selected factors that might contribute to symptom sensitivity. The pattern was very similar for both ocular and oral sensitivity.

There were no significant differences in total number of comorbidities, but oral-stoical patients were taking significantly fewer medications (of any type) than accurate patients ($p=0.002$). For both types of symptom sensitivity, stoical patients showed significantly less anxiety and depression and reported significantly higher quality of life than both sensitive and accurate patients (all $p<0.05$). There were no significant differences in anxiety and depression between the sensitive and accurate group (all $p>0.05$). There was a significant difference between the groups in the self-reported presence of functional conditions, with the sensitive group reporting a significantly higher incidence of both fibromyalgia and irritable bowel syndrome than the stoical group (all $p<0.017$). Oral-sensitive patients reported a significantly higher incidence of irritable bowel syndrome than accurate patients ($p=0.003$), but otherwise there were no further significant differences between the sensitive and accurate groups. There were no significant differences between the groups in the proportion of those with any Diagnostic and Statistical Manual- or International Classification of Disease-defined mental illness (all $p>0.05$).

To explore other factors associated with symptom sensitivity, Spearman's bivariate correlation results for both ocular and oral dryness Sensitivity are shown in table 4. Ocular Sensitivity was weakly positively correlated with number of medications and weakly negatively correlated with age, suggesting patients taking fewer medications and older patients were more stoical. Oral Sensitivity was weakly positively correlated with number of comorbidities and number of medications, suggesting those with fewer comorbidities and taking fewer medications were more stoical. Both types of Sensitivity were moderately strongly positively correlated with patient-rated symptoms, including fatigue, mental fatigue, pain, anxiety and depression. The direction of the correlations indicated that those with higher levels of these symptoms were more sensitive. Both types of Sensitivity were negatively correlated with quality of life, indicating that those with a poorer quality of life had higher Sensitivity scores.

Relationship between treatment and symptom sensitivity

To explore whether symptom sensitivity is related to treatment received, table 3 reports the proportion of patients in the different sensitivity classes that were receiving particular treatments. Ocular-stoical patients were significantly less likely to be receiving a medication known to cause dryness than sensitive patients ($p=0.004$), and whilst there was an overall group difference for oral sensitivity, post-hoc tests did not show any significant differences between the groups. There were no significant differences between the groups in use of at least one symptomatic treatment for dryness or pilocarpine (all $p>0.218$). However, oral-stoics were significantly less likely to be using a saliva substitute (40.1%) than accurate patients

(56.4%; $p < 0.001$) and there was no significant difference between stoical and sensitive patients (43.1%; $p = 0.660$). Similarly for ocular sensitivity, ocular-stoics were significant less likely than accurate patients to have received the more invasive treatments of punctal plugging or cauterisation (18.8% vs 33.8%; $p = 0.012$) and there were no differences with ocular-sensitive patients (22.0%; $p = 0.367$). Ocular-sensitive patients were significantly less likely to be using a lachrymal substitute than both the accurate and stoical patients (71.5% vs 83.1% and 82.6% respectively; $p = 0.016$ and $p = 0.002$ respectively).

Regression Analysis

Ocular Dryness

The final model contained six predictor variables and was statistically significant ($F_{6,628} = 21.8$, $p < 0.001$) explaining 16.5% of the variance in sensitivity (table 4). The statistically significant predictors in the final model were: age, disease damage index, pain, fatigue and mental fatigue. Pain explained the largest additional variance (10%) of all the predictors, with fatigue the next highest (2.3%). Age and disease damage index were both negatively related to Sensitivity, indicating older patients and those with greater disease damage tended to be less sensitive.

Oral Dryness

The final model contained six predictor variables and was statistically significant ($F_{6,628} = 24.1$, $p < 0.001$) explaining 17.9% of the variance in sensitivity (table 4). The statistically significant predictors in the final model were: use of a saliva substitute, fatigue and depression, all of which were positively associated with greater

Sensitivity. Level of fatigue explained the largest additional variance (11.7%), indicating those with higher fatigue tend to be more sensitive.

Discussion

Replicating other work, subjective dryness symptoms and objective test results were only weakly correlated in patients with PSS. Using a novel method for quantifying the discrepancy between subjective and objective symptoms, an ordinal scale of symptom sensitivity was derived that ranged from stoical (self-report dryness at a relatively low level compared to objective findings) to accurate to sensitive (self-report dryness at a relatively high level compared to objective findings). The majority of patients had a relatively stoical presentation. A significant moderate association was observed between ocular and oral dryness sensitivity, indicating that those who tended to be sensitive for ocular dryness also tended to be sensitive for oral dryness. Comparing sensitive, stoical and accurate patients found that stoical patients had lower depression and anxiety scores than the other groups, but they were also less likely to have received some treatments than accurate patients (saliva substitute, punctal plugging or cauterisation). Sensitive patients were not more likely to receive higher levels of intervention than accurate or stoical patients. They reported a higher proportion of functional conditions (fibromyalgia and irritable bowel syndrome). In regression analyses, symptom sensitivity was predicted by a variety of factors, but pain (ocular Sensitivity) and fatigue (oral Sensitivity) explained the most variance. As found in other studies, the relationship between subjective and objective measures was weaker for ocular dryness than oral dryness (35-37). Ocular dryness

sensitivity was predicted by higher pain and fatigue; whereas age and disease damage were significant negative predictors, suggesting older patients and those with more severe disease are relatively more stoical. Adata et al. (7) suggested that symptom perception may be diminished by reduced corneal sensation due to more severe illness, which may explain the negative relationship with disease damage. This may be part of the explanation why subjective and objective ocular dryness measures correlate relatively more weakly - a straightforward linear relationship between severity of disease and severity of subjective symptoms would not be expected. Additionally, fewer patients objective test results fell in the severe range for tear production (46%) compared to saliva production (77%) and 16% had objectively normal tear production (compared to only 4% for saliva production), leaving more scope to identify ocular patients as sensitive. The symptom of 'dry eye' is less well-defined than 'dry mouth' and may be used to refer to a myriad of ocular sensations including burning pain, grittiness, and tired or heavy eyes. This introduces heterogeneity between patients in what they mean when they report dry eyes and not all of the experienced sensations may be expected to relate to tear production. As 'dry eye' often refers to painful sensations in the eye, this may explain why self-report pain was the largest predictor of ocular sensitivity (but was not a significant predictor of oral sensitivity).

In contrast, sensitivity to oral dryness symptoms was most strongly-associated with global fatigue, followed by use of a saliva substitute and number of comorbidities. It was not related to disease severity or pain. This suggests that different processes are related to symptom-sensitivity to different symptoms.

The overall proportion of variance explained in both regression models (16.5-17.9%) indicates there are explanatory factors that were not included in the present study which should be explored in future studies. Biological factors relating to the composition of the tears or saliva may be of relevance. Xerostomia can be affected by saliva composition (38) and multiple factors such as lachrymal secretion, corneal damage, tear film stability and the chemical properties of tears all jointly impact on the perception of ocular dryness (39). Relatively sensitive individuals could be targeted in future research to identify biological markers in tears or saliva that may impact on perceived dryness.

Psychological models of symptom perception propose a large number of factors that may impact on whether someone notices a symptom (26) and could be of relevance to measure in PSS. Trait characteristics such as neuroticism, alexithymia (the ease with which one identifies emotions) and distress tolerance may play a role (40, 41). It has been shown that catastrophisation - a manner of thinking that exaggerates worries and amplifies negative consequences (42) - is highly predictive of pain severity in patients with PSS (43). Similarly, greater body-focused attention may contribute to symptom-noticing (44) and somatosensory amplification - a heightened responsiveness to sensory stimulation - has been shown to contribute to the symptoms of many rheumatic conditions (41). Geisser et al. (45) found that amplification in chronic fatigue syndrome and fibromyalgia was related to higher clinical pain and larger numbers of comorbid somatic symptoms and, consistent with this, we identified a higher proportion of patients with fibromyalgia in the sensitive groups. Anxiety and depression have also been shown to be significantly related to

greater sensitivity. In a population-based study by Anttila et al. (22), participants with subjective dry mouth had significantly higher frequencies of depressive symptoms.

Similarly, Kim et al. (24) concluded that depression was associated with dry eye symptoms in participants with normal Schirmer test results. Additionally, social, contextual, cultural and interpersonal factors likely also contribute to how and whether patients openly discuss their symptoms with their doctor, making it difficult to determine whether – for stoical patients particularly – they do not experience distressing symptoms or they simply do not report them.

The strengths of this study include the large sample of PSS patients and the novel method for defining sensitivity, which allowed potential associated variables to be investigated. However there are a number of limitations to acknowledge. 1) Self-report methods are prone to response bias such as demand characteristics, social desirability and recall bias (46). Furthermore, when completing the self-report measure, participants judged the severity of their sicca symptoms against their own standards; however the severity of objective measures is judged against standards formulated from the results of many individuals so a degree of discrepancy could be expected. 2) Only one objective measure of ocular and oral dryness was used. USF is described as the test of choice for assessing salivary secretion (20), however variations of methods exist for measuring ocular dryness. Whilst the Schirmer I test is a valid assessment, issues regarding reproducibility and sensitivity have been reported (47) and its use without anaesthesia (as in the present study) includes both basal and reflex lachrymal secretion (48), which may exaggerate the severity of objective ocular dryness in those with progressive corneal desensitisation.

Categories of objective symptoms were derived specifically for this study in order to calculate the sensitivity score. Whilst the expert opinion of a consultant rheumatologist was used in developing the categories and exploratory work using different cut-off scores or different ways of categorising patients showed the same pattern of relationships, the categories used here need further empirical support and replication in future studies to determine whether they can be operationalised and used clinically.

Clinical Implications and Future Research Implications

Going forward, we advocate the use of a measure of objective-subjective symptom discordance, such as outlined here, to facilitate illness stratification thereby allowing further research into the reasons behind this. Of particular interest are the groups with the greatest discordance, i.e. patients reporting severe subjective symptoms despite being at the milder end of the objective symptom distribution, and those reporting mild subjective symptoms despite being at the severe end of the objective distribution. An exploration of potential physical and psychological explanations is warranted. For example, is there a difference in pathophysiology which might contribute to the increased experience of mildly abnormal objective symptoms such as tear and saliva composition, changes in corneal sensitivity, genetic differences, e.g. in pain sensitivity. Conversely, there is a detailed literature on the psychological aspects of interoception and pain perception. Applying some of the methodologies from this literature to develop our understanding of the individual differences in the 'felt experience' of physical symptoms would allow us to explore alternative treatment options, such as Cognitive Behavioural Therapy or mindfulness for those

with lower symptom tolerance/higher subjective symptom distress (49-51).

Conclusion

The study developed a novel method for determining symptom sensitivity.

Discrepancies between objective measures and subjective symptoms were most strongly related to pain and fatigue; however, multiple interrelated psychological, pathophysiological and environmental factors are likely involved. Limitations associated with accurately measuring dry eyes/mouth both subjectively and objectively may also contribute to the observed discrepancies. Stratifying patients by symptom sensitivity for further research will improve our understanding of factors that impact on distress caused by symptoms and could open the door to non-medication-based treatments for a subgroup of patients with the highest symptom sensitivity.

Appendix 1. WFN, SJB and BG are investigators of the UKPSSR. The other UKPSSR members (as of 1 Jan 2013) include, in alphabetical order of their affiliations:

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Table 1: Severity classification groups for subjective symptoms and objective results and the grid used to derive the sensitivity score

Objective Test Results		Normal	Mild		Moderate		Severe
Schirmer I Test (mm/5min)		>14.5 (n=109; 16%)	11.5-14.5 (n=40; 6%)	8.5-11.5 (n=37; 5%)	5.5-8.5 (n=67; 10%)	2.5-5.5 (n=120; 17%)	<2.5 (n=315; 46%)
Unstimulated Salivary Flow (ml/15min)		>5 (n=26; 4%)	4-5 (n=8; 1%)	3-4 (n=9; 1%)	2-3 (n=42; 6%)	1-2 (n=74; 11%)	<1 (n=529; 77%)
Subjective Ocular/Oral Dryness Rating	0: Asymptomatic	0	-1	-2	-3	-4	-5
	1-2: Mild	1	0	-1	-2	-3	-4
	3-4	2	1	0	-1	-2	-3
	5-6: Moderate	3	2	1	0	-1	-2
	7-8	4	3	2	1	0	-1
	9-10: Severe	5	4	3	2	1	0

For example, an individual with ‘severe’ objective test results (Shirmer <2.5 or saliva flow <1) but subjectively rating themselves ‘1’ – mild would have a discrepancy classification of -4; therefore lying at the ‘stoical’ side of the distribution. An individual subjectively reporting their symptoms ‘9’ -severe, while having a ‘normal ‘ objective test would score +5; the most ‘sensitive’ side of the distribution.

Table 2: Patient characteristics/variables

	N	Mean (SD)
Demographics and Illness factors		
Age (years)	688	58.0 (12.5)
Disease Duration (months)	661	80.1 (71.5)
Symptom Duration (months)	686	152.4 (118.8)
Symptom/Diagnosis gap (months)	659	72.7 (98.6)
Number of Comorbidities	688	3.6 (2.5)
Number of medications	688	5.7 (4.1)
Patient-rated measures		
Ocular Dryness (0-10)	681	5.6 (2.8)
Oral Dryness (0-10)	681	6.0 (2.9)
Fatigue (0-10)	681	5.5 (2.7)
Mental Fatigue (0-10)	680	3.9 (2.8)
Pain (0-10)	680	4.5 (3.0)
Quality of Life – TTO (-1.0 – 1.0)	671	0.6 (0.3)
Quality of Life – VAS (0-100)	664	60.3 (21.4)
HADS Anxiety (0-21)	666	8.0 (4.6)
HADS Depression (0-21)	667	6.0 (4.0)
Clinician-rated measures		
Disease Activity Index (0 - 123)	687	4.8 (4.9)
Disease Damage Index (0 – 10)	688	2.5 (1.9)
Objective Tests		
Schirmer's test (mm/5min)	671	6.2 (7.6)
Unstimulated Salivary Flow (ml/15min)	688	0.9 (1.9)
Sensitivity		
Ocular Sensitivity (-5 to +5)	681	-0.42 (2.2)
Oral Sensitivity (-5 to +5)	681	-1.24 (1.6)

SD = Standard Deviation; TTO, Time Trade Off; VAS, Visual Analogue Scale; HADS,

Hospital Anxiety and Depression Scales

Table 3: Mean comorbidities, number of medications and scores for depression, anxiety and quality of life by dryness sensitivity classification. Proportions of patients in the different groups with specific comorbidities and receiving particular treatments.

	Ocular Sensitivity				Oral Sensitivity			
	Stoical (n=351)	Accurate (n=130)	Sensitive (n=200)	Comparison	Stoical (n=444)	Accurate (n=179)	Sensitive (n=58)	Comparison
# Comorbidities	3.4 (2.3)	3.9 (2.5)	3.8 (2.6)	$F_{2,678}=2.90, p=0.056$	3.4 (2.3)	3.8 (2.6)	3.9 (2.7)	$F_{2,678}=9.5, p=0.078$
# Medications	5.5 (4.1)	5.7 (3.7)	6.3 (4.2)	$F_{2,678}=2.52, p=0.081$	5.4 (3.9) ^a	6.6 (4.5) ^b	5.8 (3.9) ^{a,b}	$F_{2,678}=4.97, p=0.007$
Anxiety (HADS)	7.3 (4.5) ^a	8.4 (4.8) ^b	8.9 (4.4) ^b	$F_{2,661}=8.75, p<0.001$	7.3 (4.4) ^a	9.0 (4.8) ^b	10.2 (4.0) ^b	$F_{2,661}=16.45, p<0.001$
Depression (HADS)	5.3 (3.7) ^a	6.4 (4.3) ^b	6.9 (4.3) ^b	$F_{2,661}=11.23, p<0.001$	5.2 (3.6) ^a	7.2 (4.4) ^b	8.1 (4.3) ^b	$F_{2,661}=24.00, p<0.001$
Quality of Life (VAS)	63.8(20.6) ^a	56.6(22.5) ^b	56.3(21.2) ^b	$F_{2,659}=10.09, p<0.001$	63.4(20.2) ^a	54.3(22.5) ^b	53.9(22.7) ^b	$F_{2,659}=14.14, p<0.001$
Specific comorbidities								
Fibromyalgia (%)	6.3 ^b	8.5 ^{a,b}	14.0 ^a	$X^2(2)=9.39, p=0.009$	7.0 ^b	11.2 ^{a,b}	17.2 ^a	$X^2(2)=8.08, p=0.018$
IBS (%)	5.4 ^b	7.7 ^{a,b}	12.0 ^a	$X^2(2)=7.70, p=0.021$	7.7 ^b	5.0 ^b	17.2 ^a	$X^2(2)=9.13, p=0.010$
Mental Illness (%)	3.1	6.2	4.0	$X^2(2)=2.27, p=0.321$	2.7	6.7	5.2	$X^2(2)=5.61, p=0.061$
Treatments								
Use of xerogenic medication (%)	37.3 ^a	46.2 ^{a,b}	50.0 ^b	$X^2(2)=9.14, p=0.010$	39.2	48.6	51.7	$X^2(2)=6.72, p=0.035$
Use of symptomatic treatment for dryness (%)	97.7	96.9	97.5	$X^2(2)=0.25, p=0.883$	97.1	97.8	100.0	$X^2(2)=1.875, p=0.392$
Pilocarpine (%)	7.1	9.2	7.5	$X^2(2)=0.61, p=0.739$	7.2	10.1	3.4	$X^2(2)=3.04, p=0.218$
Saliva substitute (%)	-	-	-	-	40.1 ^a	56.4 ^b	43.1 ^{a,b}	$X^2(2)=13.83, p=0.001$
Lachrymal substitute (%)	82.6 ^b	83.1 ^b	71.5 ^a	$X^2(2)=10.95, p=0.004$	-	-	-	-
Punctal plugging or Cauterisation (%)	18.8 ^a	33.8 ^b	22.0 ^{a,b}	$X^2(2)=12.33, p=0.002$	-	-	-	-

#, number; HADS, Hospital Anxiety and Depression Scales; VAS, Visual Analogue Scale; IBS, Irritable Bowel Syndrome; groups with different superscripts show significant differences from one another in post-hoc tests (p<0.05 for continuous measures, p<0.017 for categorical)

Table 4: Spearman's (r_s) Bivariate Correlations between sensitivity

	Ocular Sensitivity	Oral Sensitivity
Demographic and Illness Factors		
Age	-0.11***	-0.02
Disease Duration	0.02	0.07
Symptom Duration	-0.00	0.03
Number of Comorbidities	0.07	0.11**
Number of Medications	0.10**	0.12**
Patient-rated measures		
Fatigue	0.38***	0.39***
Mental Fatigue	0.33***	0.30***
Pain	0.33***	0.29***
Quality of Life – Time Trade Off	-0.25***	-0.24***
Quality of Life – Visual Analogue Scale	-0.21***	-0.28***
HADS Anxiety	0.20***	0.26***
HADS Depression	0.22***	0.30***
Clinician-rated Measures		
Disease Activity Index	0.02	0.03
Disease Damage Index	-0.07	0.05
Oral Sensitivity	0.35***	-

* 0.01<math>p\leq 0.05, ** 0.001<math>p\leq 0.01, *** $p\leq 0.001$

HADS, Hospital Anxiety and Depression Scales

Table 5: Stepwise hierarchical regression summary for ocular dryness sensitivity and oral dryness sensitivity

Model	Adjusted R ² (%)	ΔR ² (%)	Standardised Beta	Test- statistic	p
Ocular Dryness Sensitivity					
<u>Overall Model</u>	16.5	-	-	F _{6,628} =21.8	<0.001***
Age		1.3	-0.09	t ₆₃₄ =-2.39	0.017*
Number of medications		1.9	0.01	t ₆₃₄ =0.25	0.802
Disease Damage Index		0.5	-0.08	t ₆₃₄ =-2.23	0.026*
Pain		10.0	0.19	t ₆₃₄ =3.89	<0.001***
Fatigue		2.3	0.16	t ₆₃₄ =2.95	0.003***
Mental Fatigue		0.5	0.11	t ₆₃₄ =2.14	0.033*
Oral Dryness Sensitivity					
<u>Overall Model</u>	17.9	-	-	F _{6,628} =24.1	<0.001***
Use of a saliva substitute	-	2.9	0.15	t ₆₃₄ =3.99	<0.001***
Number of comorbidities	-	1.3	0.02	t ₆₃₄ =0.43	0.667
Age	-	0.6	-0.01	t ₆₃₄ =-0.21	0.831
Xerogenic medications	-	0.5	0.01	t ₆₃₄ =0.24	0.812
Fatigue	-	11.7	0.30	t ₆₃₄ =6.88	<0.001***
Depression	-	0.9	0.13	t ₆₃₄ =2.91	0.004***

* 0.01<p≤0.05, ** 0.001<p≤0.01, ***p≤0.001

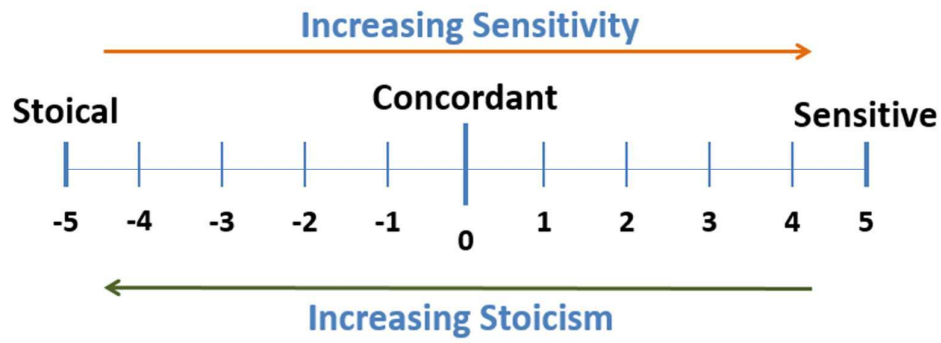


Figure 1: Sensitivity Scale